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## Optimizing treatment with psychotropic agents through precision drug therapy

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## SUMMARY

For the application of precision drug therapy, physicians have an increasing set of tools which can be used to individualize drug therapy. Pharmacogenetics information is one of these tools. One of the applications of pharmacogenetic information is prediction of drug metabolizing capacity. Nevertheless, for precision drug therapy both internal factors, like pharmacogenetics, and external variations need to be considered.

As was shown in chapter 2, precision drug therapy is important, because several environmental and genetic variations can influence drug exposure. That these differences in exposure are substantial is illustrated in Chapter 2.1. in which an unexpected rise in plasma concentration of clozapine was found when the dose of clozapine was actually decreased. The observed discrepancy was likely due to a change in smoking behavior of the patient. In Chapter 2.2. the relation between genetic differences in the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6) and observed CYP2D6 activity was studied. Age (60-75 years vs. >75 years) or gender were not identified as risks factor for phenoconversion towards a lower metabolic activity. However, male subjects treated with venlafaxine had more change on phenoconversion towards a higher metabolic activity. As a result, most genetically IMs who used venlafaxine, had an EM phenotype. Based on these findings, it can be concluded, that old age does not have to be considered as an additional reason for dose adaptations among IMs treated with venlafaxine. On the other hand, PM phenotypes were found to be reliably predicted based on genotype. In addition, a lower response to the antidepressants was found on the Hamilton Rating Scale for Depression for PMs, although this did not reach significances when measured on the Montgomery Åsberg Depression Rating Scale. It was concluded that genotyping for CYP2D6 can be used as a reliable tool in old age psychiatry to predict PM phenotypes which could be related to a higher risk for non-response. A lower dose should be given to these patients and their plasma concentrations should be carefully monitored to ensure that they are within the therapeutic range.

Plasma concentrations of nortriptyline and venlafaxine are usually monitored in blood collected by a venipuncture. To individualize TDM, a more patient friendly alternative is described in this thesis. This alternative included dried blood spot (DBS) sampling in which droplets of blood are obtained by a fingerprick and spotted onto paper. A small piece of this paper is analyzed to assess the concentrations of the antidepressants. Besides patients comfort, DBS have more advantages. The stability of the analyte is usually high and samples can be sent with normal post services due to the low biohazard risks of dried blood. Consequently, patients do not have to travel to a laboratory, because samples can be collected at the psychiatrist office or at home. In Chapter 3.1. and 3.2. results of analytical validation are described for DBS analysis with

the use of liquid chromatography-tandem mass spectrometry (LC-MS/MS). Methods for six tricyclic antidepressants (TCAs), venlafaxine (VFX) and *O*-desmethylvenlafaxine (ODV), were validated. Validation was performed according to requirements of guidelines and except for clomipramine (CMP) and desmethylclomipramine (DCMP) criteria were met. For CMP and DCMP the lower limit of quantification was increased from 20 to 40 µg/L to comply with the guidelines criteria. In chapter 3.3. results of a clinical validation of DBS analyses is described. Paired plasma and DBS samples were collected from 162 patients. Evidence for proportional differences between plasma and DBS concentrations, which were identified in chapter 3.1. and 3.2., were confirmed in chapter 3.3. To be able to link DBS to plasma concentrations a translation factor was calculated based on Passing and Bablok regression analysis. DBS concentrations were found related to plasma concentrations by a factor of 1.22, 0.8, 0.65, 0.84, and 0.78 for amitriptyline (ATP), nortriptyline (NTP), DCMP, VFX, and ODV, respectively. For CMP, no reliable factor could be identified, due to substantial bias in the analysis. Evidence was found that the factor of ATP was sensitive to variations of the hematocrit of the DBS which was analyzed by potassium based hematocrit analysis. Further research is needed for quantification of the translation factors of ATP and CMP. We applied the translation factors on the datasets and we compared the clinical interpretation of the plasma and DBS derived plasma concentrations. We found interpretation was in agreement for 96%, 97%, 75% and 100% of the observations for the sum of ATP & NTP, NTP, the sum of CMP & DCMP and the sum of VEN & ODV, respectively. Again, the results for the sum of CMP & DCMP were inadequate compared to the other compounds. To give a clear cut-off for differences between plasma and DBS derived plasma concentrations, criteria were calculated based on guidelines limits for accuracy and precision of bioanalytical methods. A Monte Carlo simulation was performed to simulate 10,000 method comparison studies on the borderline of acceptance criteria. We found that based on the bias between plasma and DBS derived plasma concentrations of individual data points no more than 5% of the samples should have a bias >36% at concentrations above the quality control low (QCL) level. For data points with concentrations between the LLOQ and QCL, no more than 5% of the samples should have a bias > 48%. These criteria were applied on additional samples of nortriptyline and criteria were met. As such, TDM of NTP by DBS was validated according to these new criteria. Criteria for acceptance of clinical method comparison studies should be issued by bioanalytical guidelines, these criteria should include clinical comparability and biases of individual data points. For the later, limits presented in this thesis can be used.

In chapter 4 of this thesis, economic evaluations of pharmacogenetic testing were studied. In chapter 4.1. a systematic review is described to study outcomes, quality and shortcomings of economic evaluations of pharmacogenetics testing. The last decade an increase in the number of studies and in the reporting of quality associated

characteristics was observed. To improve future evaluations, scenario analysis including a broad range of PGx tests costs and equal costs of comparator drugs to assess the intrinsic value of the PGx tests, were recommended. In addition, the lack of robust clinical evidence regarding PGx tests' efficacy was identified as an important limitation of economic evaluations.

Cost-effectiveness analyses of genotyping for CYP enzymes in combination with antidepressants were not found in the review. Nevertheless, the relation between exposure of nortriptyline and differences in *CYP2D6* genotypes are well-established. Guidelines for dose recommendations are issued by international and national institutes and should be considered when pre-emptive genotyping is performed. However no guidance is available whether such an approach would be cost-effective. Therefore, a cost-effectiveness analysis was performed to assess if routine genotyping, in addition to TDM, for all patients who start nortriptyline pharmacotherapy in a clinical setting would be cost-effective. Genotyping costs were determined based on screening for five mutations (~€200 per test) of which clinical effects were reported based on a pharmacokinetic modelling study. It was found that routine genotyping is not a cost-effective strategy (€50 000 per quality adjusted life year gained), unless genotyping costs are reduced towards €40 per test. Interestingly, it was found that including dose adaptations for IMs, would decrease the cost-effectiveness of genotyping due to the relatively high risk that patients with an IM genotype express an EM phenotype. As such, a dose which is too low would be given to these patients which was assumed to result in a delayed response to the antidepressant and therefore a lower quality of life. This lower quality of life resulted in a lower cost-effectiveness. Our estimates contain substantial uncertainty, mainly due to the lack of hard clinical evidence that genotyping can indeed prevent sub- or supratherapeutic plasma concentrations of nortriptyline. It is important that effects of genotyping are studied in a study design with a small change on biased outcomes, for which a randomized controlled trial (RCT) is currently still considered the best study design. Therefore a RCT was designed and is conducted. The design of the Cyp Screening Elderly (CYSCE) trial is described in chapter 4.3. Inclusion of patients started in 2013. While this thesis is written, inclusion of patients in the trial is still ongoing. Results of this trial will help to inform clinicians and decision makers about the added value of genotyping for *CYP2D6* among elderly patients who start nortriptyline and venlafaxine pharmacotherapy.

In conclusion, different efforts to optimize pharmacotherapy with psychotropic drugs were described in this thesis. DBS analysis was implemented for TDM of nortriptyline and venlafaxine in the CYSCE trial and as such centralized TDM of a national multicentre trial was realized. Based on a pharmacoeconomic model it was concluded that genotyping of *CYP2D6* in addition to TDM was not cost-effective in nortriptyline pharmacotherapy at current genotyping costs. It was cost-effective at test costs of

€40 per test. However, these estimates contain substantial uncertainty. Results of the CYSCE trial, which will be available in the near future will help to reduce this uncertainty. With ongoing developments like lower genotyping costs due to improved technology, better knowledge of the relation between genotype and phenotypes and multi-gene-approaches, precision drug therapy of psychotropic medicine facilitated by genetic information is within reach. Although, future research is needed to study bottlenecks which hamper implementation. Moreover, harmonization is needed on a regional and national level about which patients should be genotyped, for what kind of variations, when genotyping should be performed and how to document the results.